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National Advisory Mental Health Council

Minutes of the 201st Meeting

September 13, 2002

Minutes of the 201st Meeting
of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 201st meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on September 12, 2002, in Conference Room C/D/E of the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 4:45 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at 8:40 a.m. on September 13, 2002, in Building 1, Wilson Hall, at the main campus of the National Institutes of Health (NIH) in Bethesda, Maryland. In accordance with Public Law 92-463, this policy meeting was open to the public until its adjournment at 1:00 p.m. Richard K. Nakamura, Ph.D., Acting Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at Closed and/or Open Sessions (see Appendix B for Council Roster):

Mary L. Durham, Ph.D.
Javier I. Escobar, M.D.
Susan Folkman, Ph.D.
Megan R. Gunnar, Ph.D.
Henry A. Lester, Ph.D.
Jeffrey A. Lieberman, M.D.
James L. McClelland, Ph.D.
James P. McNulty
Charles B. Nemeroff, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
Elaine Sanders-Bush, Ph.D.
Edward Scolnick, M.D.
Larry R. Squire, Ph.D.
Ming T. Tsuang, M.D., Ph.D.
Roy C. Wilson, M.D.

Chairperson

Richard K. Nakamura, Ph.D.

Executive Secretary

Jane A. Steinberg, Ph.D.

Ex-Officio Council Members Present at Closed and/or Open Sessions:

Elias A. Zerhouni, M.D., Director, National Institutes of Health
Robert Freedman, M.D., Department of Veterans Affairs
Elspeth Cameron Ritchie, M.D., Department of Defense

Liaison Representative, Substance Abuse and Mental Health Services Administration

Michael English, J.D., Center for Mental Health Services

Others Present at Open Policy Session:

Thomas Aigner, National Institute on Drug Abuse
Janet Aker, "*The Blue Sheet"*
Doreen Bell, Depression and Bipolar Support Alliance
Ruth Benca, Sleep Research Society
John Bird, American Association for Marriage and Family Therapy
Dan Dolan, U.S. Department of State
Cynthia Folcarelli, National Mental Health Association
Don Fowles, Academy of Psychological Clinical Science
Marilyn Goldstein, National Education Alliance for Borderline Personality Disorder
Josh Grant, National Association of School Psychologists
Sally T. Hillsman, American Sociological Association
Perry Hoffman, National Education Alliance for Borderline Personality Disorder
Gail Hutchings, Center for Mental Health Services
Michael Iadarola, National Institute of Dental and Craniofacial Research
Thomas Insel, Emory University
Toni Johns, *The Federal Paper*
Beth Kaplanek, Children and Adults with Attention-Deficit/Hyperactivity Disorder
Gary Kennedy, American Association for Geriatric Psychiatry
Alan Kraut, American Psychological Society
Christine Lehmann, American Psychiatric Association
Molly Melvin, AARP Public Policy Institute
Kathleen Michels, Fogarty International Center
Pam Moore, Capitol Publications, Inc.
William Narrow, American Psychiatric Association
Dixianne Penney, National Education Alliance for Borderline Personality Disorder
Valerie Porr, Treatment and Research Advancements Association for Personality Disorder (TARA APD)
Stephanie Reed, American Association for Geriatric Psychiatry
Darrell Regier, American Psychiatric Association
Mary Ruffolo, Society for Social Work and Research, University of Michigan
Kurt Salsinger, American Psychological Association
Jeremy Scott, Tourette Syndrome Association, Inc.
Angela Sharpe, Consortium of Social Science Associations
Heidi Splete, *Clinical Psychiatry News*
Hollie Stephenson, Society for Neuroscience
Karen Studwell, American Psychological Association
Sheldon Weinberg, The CDM Group, Inc.
Susan Weiss, National Institute on Drug Abuse
Joan Levy Zlotnik, Institute for the Advancement of Social Work Research

OPEN POLICY SESSION: Call to Order

Richard K. Nakamura, Ph.D., Acting Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 201st Council meeting at 8:40 a.m. on September 13, 2002, in

Building 1, Wilson Hall, on the campus of NIH in Bethesda, Maryland. After welcoming those present, Dr. Nakamura announced that the next Director of NIMH, Dr. Thomas Insel, was present and would be formally introduced during the course of the meeting by Dr. Elias Zerhouni, Director, NIH.

NIMH ACTING DIRECTOR'S REPORT

Referring to his written Acting Director's Report, Dr. Nakamura first noted two key personnel changes that have taken place at the Institute—the resignation of Dr. Steven Hyman as NIMH Director that led to Dr. Nakamura's appointment as Acting Director of NIMH; and the detail to NIMH of Dr. Bernard Arons, former Director of the Center for Mental Health Services (CMHS), a component of the Substance Abuse and Mental Health Services Administration (SAMHSA), who recently resigned from that position. Dr. Arons brings to the institute an expertise in translating research findings into practice, a major focus area for the Institute. Dr. Nakamura also noted that Ms. Gail Hutchings will serve as Acting Director of CMHS, a Center charged with providing leadership for delivering mental health services, for generating and applying new knowledge, and for establishing national mental health policy.

Dr. Nakamura next reported on several changes in the scientific staff at NIMH. In the Director's Office, Dr. Michael Sesma joined the Office for Special Populations as Chief of the Mental Health Research Scientist Development Program. Dr. Alicia Dustira accepted a position in the Office of Science Policy and Program Planning as Planning and Evaluation Officer. Dr. LeShawndra Price was appointed as a Psychologist in the Developmental Psychopathology and Prevention Research Branch of the Division of Mental Disorders, Behavioral Research and AIDS (DMDBA). Dr. Regina Smith James is a new Medical and Program Officer for the Child and Adolescent Attentional Disorders Program in the Developmental Psychopathology and Prevention Research Branch of DMDBA. Dr. Audrey Thurm has joined the extramural staff as a program specialist with responsibilities related primarily to autism in both the Division of Neuroscience and Basic Behavioral Science (DNBBS) and DMDBA. Finally, Dr. Kazutoshi Nakazawa accepted a tenure track position in the Mood and Anxiety Disorders Research Branch of the Division of Intramural Research Programs (IRP).

Significant changes are taking place in the Council membership as well. Dr. Nakamura acknowledged the four members whose terms will expire on September 30, 2002, and presented commemorative plaques to Drs. Mary Durham, Charles Nemeroff, and Roy Wilson, noting that the fourth member, Dr. Edward Scolnick, was unable to be at the policy session. The four new Council members who will be attending the January 2003 Council meeting are:

- Susan M. Essock, Ph.D., Professor, Department of Psychiatry, and Director, Division of Health Services Research in the Department of Psychiatry at Mt. Sinai School of Medicine, New York.
- Renata J. Henry, M.Ed., Director of the Division of Substance Abuse and Mental Health, Delaware Health and Social Services, in New Castle, Delaware.
- Charles F. Reynolds, III, M.D., Professor of Psychiatry, Neurology, and Neuroscience in the Department of Psychiatry, School of Medicine, University of Pittsburgh, and Senior Associate Dean of that School. Dr. Reynolds also directs the Mental Health Intervention

Research Center for Late-Life Mood Disorders at the Western Psychiatric Institute and Clinic.

- Karen D. Wagner, M.D., Ph.D., Clarence Ross Miller Professor and Vice Chair of the Department of Psychiatry and Behavioral Sciences at the University of Texas Medical Branch in Galveston, Texas, where she also directs the Division of Child and Adolescent Psychiatry.

Approval of the Minutes of the Previous Council Meeting

Dr. Nakamura requested and received a motion to approve the minutes of the May 10, 2002, NAMHC meeting, which passed unanimously without further discussion.

Collaboration Between NIMH and CMHS/SAMHSA

Over the past year, Dr. Nakamura continued, increasing attention has focused on moving science to service—that is, translating research results into effective mental health treatments for patients in non-research settings. Since Dr. Charles Curie became Administrator of SAMHSA in November 2001, Dr. Wayne Fenton at NIMH and Ms. Gail Hutchings at CMHS/SAMHSA have been working together to develop an overall agenda to facilitate the exchange of information between NIMH and CMHS. There is widespread agreement that service delivery systems and policies must be considered in designing research that is relevant to practitioners and consumers who need a steady flow of high-quality information upon which to make mental health treatment and service decisions. This emphasis on close collaboration began during the tenures of Drs. Bernard Arons and Thomas Bornemann at SAMHSA, and Dr. Nakamura commented that increased communication/exchange between NIMH and CMHS/SAMHSA remains a priority for the current leadership.

President's New Freedom Commission on Mental Health

When President Bush pledged support last April for obtaining parity for mental health insurance coverage, he expressed his heart-felt belief that mental illnesses are real, diagnosable, and treatable and that the Nation has a responsibility to deliver adequate and appropriate mental health services to those who need them. He then announced the creation of the President's New Freedom Commission on Mental Health, a Commission that had a 1-year mission to conduct a comprehensive study of the U.S. mental health service delivery system and to make recommendations for improving the system (see http://www.mentalhealthcommission.gov/). This forum offers an excellent opportunity to examine mental health service delivery systems and to make an impact on their functioning. Dr. Nakamura urged all Council members to contact the Commission directly—in person or through the Web site—and to provide comments or anecdotes about how well or poorly mental health service systems are performing and what can be done to improve them. Also, Dr. Nakamura added, it will be important for constituency groups and others to provide thoughtful and useful suggestions to the Commission. He noted that Council member Dr. Norwood Knight-Richardson serves on the Commission, which is staffed by SAMHSA, and that the next Council meeting would likely include an interim report on the work of the Commission.

Support for Clinical Scientists

In response to a crisis in the field, NIMH has devoted considerable attention to encouraging the development of clinical scientists. It has been particularly difficult to recruit physician scientists—to get top students from medical schools to become mental health researchers. Coping with heavy financial obligations seems to be a major deterrent to committing to research. To address this problem, NIH announced a series of extramural loan repayment programs (LRP) that can repay up to $35,000 annually toward the outstanding eligible educational debt of LRP participants (see http://www.lrp.nih.gov/NIHLRP/about/extramural/extramural_faq.htm). NIMH has just completed the first round of loan repayments, voluntarily assuming 10 percent of the loan repayment slots although the Institute represents only 5 percent of all eligible NIH applicants. This was done to ensure that mental health clinicians receive maximum loan repayment relief as well as maximum encouragement to start research careers. The Institute's clinical career development program also has successfully supported new clinical researchers. Additionally, the field has enthusiastically endorsed the increased $250,000 limit for R25 mental health education grants, which are targeted toward clinical scientists.

In collaboration with the Institute of Medicine, NIMH has been trying to get a clinical research track approved as part of credentialing for psychiatry residents so that they can receive research training while they are completing their degrees. Dr. Wayne Fenton has been leading the Institute's efforts on that initiative. NIMH also has been discussing training issues with the American Academy of Clinical Psychologists to make certain that new psychologists receive up-to-date information about developments in neuroscience and behavioral science.

Dr. Nakamura concluded discussion of these new initiatives by noting that there is a changing climate at NIH. In tandem with commitments to double the NIH budget, Congress is asking how the increased monies are being utilized. Dr. Nakamura commented that NIMH continues its planning process to design a research agenda and an outcome-based evaluation process that will clearly articulate target goals, how they can be measured, and when they might be accomplished. Budget projections and adjustments will be based on how well target goals are met. Council members and constituency groups remain a vital part of this planning process and are strongly encouraged to participate.

Acknowledgment of Support

At the conclusion of his remarks, Dr. Nakamura reminded the audience that this was his last Council meeting as Acting Director and extended appreciation to all those who had helped him during his brief tenure in this position. He expressed particular gratitude for the contributions of Dr. Fenton, the Acting Deputy Director, NIMH; Dr. Jane Steinberg, Executive Secretary to Council and Director, Division of Extramural Activities (DEA); all of the dedicated Council members; the responsive NIMH staff; and the many constituency groups. He was proud, he said, to be a part of NIMH, an organization dedicated to reducing the burden of mental illness through research.

THE NIMH INTRAMURAL RESEARCH PROGRAM (IRP)

Overview

Dr. Robert Desimone, Scientific Director of the IRP, updated Council about ongoing activities to revitalize the IRP. In recent months, new scientists have been recruited to lead programs in the areas of human bipolar genetics, animal neurogenetics, and the much understudied areas of psychopathy and other severe personality disorders. Additionally, two very special instruments have been delivered that will increase NIMH's scientific capabilities in the area of brain imaging in mental illness. The new magnetoencephalography (MEG) machine has a very high temporal resolution—on the order of milliseconds—and the potential, when combined with functional magnetic resonance imaging (fMRI), of providing high spatial and temporal resolution of neural activity in brain imaging. This new instrument is shared with the National Institute of Neurological Disorders and Stroke (NINDS), and the two institutes have joined a consortium of scientists from Harvard University, the University of Minnesota, and Los Alamos National Laboratory to develop the needed tools for combining data from these techniques.

The second new instrument is a vertical-bore monkey MRI that allows noninvasive brain imaging data to be collected from awake, behaving monkeys sitting in a natural upright position and performing cognitive tasks. This will facilitate grounding the findings from human brain imaging in basic neurobiology. In a joint venture, NIMH, NINDS, and the National Eye Institute will share both costs and available talent for developing this technology.

These new additions to the IRP strengthen a program that already has significant capabilities; one of the most exciting of these is the schizophrenia program that is headed by Dr. Daniel R. Weinberger, Chief of the Clinical Brain Disorders Branch. Among the seminal findings of Dr. Weinberger and his colleagues is the key role played in the pathophysiology of schizophrenia by the brain axis that extends from the medial temporal lobe, through the basal ganglia, and into the prefrontal cortex. A recent review of this Branch by the Board of Scientific Counselors found that the investigators' work on schizophrenia, which combines brain imaging, postmortem work, genetics, molecular biology, and neuropharmacology, is unique in its wide-ranging but integrated approach. Dr. Desimone then introduced Dr. Weinberger as the next speaker who would describe the first application of functional brain imaging to genetically define subgroups of both healthy volunteer control subjects and patients with schizophrenia. This is crucial, Dr. Desimone noted, because diseases such as schizophrenia likely involve pathologies of several different brain systems that share a common behavioral phenotype. Moreover, this integrated approach has the potential, as Dr. Weinberger's recent article in *Science* reflects (see http://www.sciencemag.org/cgi/content/full/297/5580/400), to offer insights about the underlying biology of normal human temperament and personality as well as the underlying biology of schizophrenia.

Imaging Genomics

Dr. Weinberger, Chief of the Clinical Brain Disorders Branch, IRP, speaking on the topic of "Imaging Genomics: Making Sense of Susceptibility Genes for Mental Illness," described a research paradigm that combines clinical genetics and neuroimaging in attempts to increase an understanding of how, at the level of clinical brain biology, genes increase susceptibility to the manifestations of mental illness.

Two questions, Dr. Weinberger said, capture some of the confusion and difficulties that have plagued our thinking about genes and mental illness for a long time: Why are genes for psychiatric disorders so hard to find, and why are genetic mechanisms of susceptibility so difficult to identify? One answer to these questions is that genes do not encode for psychopathology—for hallucinations, delusions, thought disorganization, panic attack, or depression. Because there is a very complex relationship between how variation in a gene affects its regulation and the function of its products and, ultimately, how cells process molecular information, there is a very complicated pathway from effects at the molecular/cellular level to the emergent behavioral phenomenon of mental illness. This path is not easy to reconstruct. However, neuroimaging is being applied to disentangle this complex pathway on the assumption that studying gene effects at the molecular/cellular level of information processing in the brain will show greater effect sizes of the biology of these gene variations.

Dr. Weinberger next described how three genes that have been the focus of many psychiatric studies illustrate this paradigm. The most extensively studied gene is catechol-o-methyl transferase (COMT), an enzyme that methylates such catechol structures as norepinephrine, dopamine, and estrogen. It was first discovered in 1958 at NIMH by Dr. Julius Axelrod, who won a Nobel Prize for his efforts. Dr. Weinberger's laboratory was very interested in a common variation in this gene: a single nucleotide polymorphism in the fourth axon of the gene that changes the amino acid sequence in the translated protein. The polymorphism has a profound effect on the enzyme activity of this protein. The polymorphism is not a marker allele but a highly functional genetic variation that impacts the biological activity of this protein: individuals who inherit methionine *(met*) alleles at this locus in the amino acid sequence from their parents have about one-fourth of the COMT enzyme activity of individuals who inherit valine (*val*) alleles. To illustrate the confusion that can exist in psychiatric genetics, one only has to look at the clinical associations that have been reported inconsistently with various alleles of this gene. While COMT cannot possibly account for all the variability in psychopathology, it is conceivable that there is a biology of variation in COMT activity, inherited because of this genetic variation, that impacts brain systems and underlies emergent behavioral phenomena representing this behavioral spectrum.

To address the question of whether inherited variations of this gene can impact its biology, it is important to appreciate the biology of COMT at the level of brain function. Abundant evidence, first developed in Dr. Richard Wyatt's laboratory at NIMH, demonstrates that COMT has a unique impact on dopamine signaling in prefrontal cortical synapses (see "Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia" available at http://www.pnas.org.cgi/content/full/98/12/6917). This finding has been shown in pharmacological studies with humans and rodents that examine improvements in prefrontal

cognitive function based on COMT inhibition. More recently, this finding has been shown with genetically engineered mice that lack COMT.

COMT function is uniquely relevant to dopamine signaling at prefrontal cortical synapses, not because COMT is found only at prefrontal cortical synapses, but because dopamine signaling elsewhere is mostly inactivated by high-capacity transporter reuptake. Actually, dopamine transporters are not very abundant in the prefrontal cortex, and they play virtually no role in dopamine signaling in the prefrontal cortex. Thus, it is predicted that variations in COMT activities, which could be caused by many things but are described here in the context of inheritance, would impact the biology of information processing in the prefrontal cortex mediated by dopamine signaling. A large body of basic scientific literature, pioneered in Dr. Patricia Goldman-Rakic's laboratory at Yale, supports the argument that dopamine signaling in the prefrontal cortex modulates the signal-to-noise characteristics of prefrontal information processing within a fairly narrow window of dopamine signaling.

Because COMT activity is clearly a variable in the modulation of dopamine signaling in the prefrontal cortex and in the resulting functional output of the prefrontal cortex, an individual's genotype—the alleles inherited from each parent—predicts placement on the inverted U-shaped curve that Dr. Goldman-Rakic and others have argued characterizes the functional impact of dopamine signaling in the prefrontal cortex. It could be predicted that individuals who inherit valine alleles from each parent (*val/val* genotype)—those individuals having four times the enzyme activity of individuals who inherit methionine alleles from each parent (*met/met*)—would have the poorest prefrontal cortical function—or the least signal-to-noise response for mediating this kind of information. Individuals with *val/met* genotypes, who inherit one allele from each parent, would have intermediate prefrontal functioning while those with methionine homozygous genotypes (*met/met*) have optimum prefrontal functioning.

Using fMRI to demonstrate the efficiency with which information is processed in the cortex—or the amount of brain machinery needed for a given level of performance accuracy—Dr. Weinberger illustrated the predicted COMT genotype effects on the efficiency of prefrontal cortical function with slides showing how normal subjects respond to a working memory task. He presented data that depicted how individuals with *val/val* genotypes process the information less efficiently than individuals with *val/met* genotypes, and, consistent with the allele load effect that would be predicted by the biology of this gene, individuals with *met/met* genotypes are most efficient at handling this information. This same allele load-dependent relationship between *val* and *met* allele genotypes in the prefrontal cortex and the efficiency with which prefrontal cortical information is processed has now been observed in at least four independent samples of healthy volunteers studied by investigators in the Clinical Brain Disorders Branch. All the studies concluded that differences in the signal-to-noise characteristics of the prefrontal cortex during information processing are related to an individual's relative baseline position, based on genetic background, on the inverted U-shaped curve—with *val/val* individuals being less efficient because they do not have optimum dopamine signaling and are lower on the curve, while *met/met* individuals are most efficient because they have optimum dopamine signaling and are at the peak of the curve.

Dr. Weinberger stated that to further substantiate the validity of this assumption of an inverted U curve in dopamine impact on prefrontal cortex function, the location of individuals on this inverted U curve can be manipulated pharmacologically by the administration of amphetamine or by varying the load of information processing in the prefrontal cortex by increasing working memory load. For *val/val* individuals, amphetamine in prefrontal cortex increases dopamine signaling by blocking norepinephrine transporters, which changes the concentration gradients that control diffusion of dopamine out of the synapse. The prediction that individuals with *val/val* genotypes who are given an increased working memory load and amphetamine will have increased dopamine signaling and will shift to a more optimal efficiency level in terms of information processing, looking more like *met/met* individuals on placebo. At the same time, *met/met* individuals with normally optimum dopamine signaling will lose efficiency in prefrontal cortex function when given an increased working memory load and amphetamine. Thus, Dr. Weinberger concluded, there is an interaction of working memory load, amphetamine, and genotype in the dorsal lateral prefrontal cortex, a critical node for information processing. Referring to graphs, Dr. Weinberger explained what would be predicted by the U-shaped relationships. That is, at all load levels on placebo, individuals with *met/met* genotypes process the same information more efficiently than individuals with *val/val* or *val/met* genotypes while individuals with *val/val* genotypes process information more efficiently when they are on amphetamine than when they are not. Interestingly, the efficiency of information processing among *met/met* individuals actually deteriorates at high working memory load and on amphetamines.

Dr. Weinberger said that these studies suggest that the COMP $val^{158/108}met$ genotype affects the efficiency—the neural signal-to-noise—of prefrontal cortical information processing in humans. These are probably the first studies demonstrating a specific genetic mechanism of variation in specific human cognitive functioning. Since first reported about 2 years ago by Dr. Weinberger's laboratory, this relationship between COMT genotype and prefrontal cognition has been confirmed by six other independent groups of investigators. One of the more fascinating observations with potential clinical implications is that one contributing variable to the outcome of amphetamine treatment may be COMT genotype: individuals with *met/met* genotypes are at increased risk for an adverse brain response to amphetamine.

Another gene that has been the focus of much interest in psychiatry is the gene for the serotonin transporter protein. This transporter protein is the target for selective serotonin reuptake inhibitors (SSRIs)—medications such as fluoxetine (Prozac) that are used to treat a variety of depression and anxiety disorders. A common polymorphism in the promoter sequence of this gene, a repeat sequence, has been studied as a potential functional factor in the expression of the mature transporter protein. Two common forms of this promoter variant that represent short or long numbers of tandem repeats have shown in tissue culture studies that individuals who are short allele carriers (S) have less activity and expression of serotonin transporters *in vitro.* Dr. Weinberger said that this result suggests that there is a functional variation in the promoter sequence, at least *in vitro.*

Dr. Weinberger's laboratory reported on its first imaging genomics study about 2 years ago, finding a similar effect of this variation in living human beings. When his group used SPECT imaging to study the expression of the actual transporter protein in living human beings by

quantifying the binding affinity of a radio-ligand in the raphe nucleus to this protein, it found almost identical relationships between expression of transporter in S-carriers and L/L-homozygous healthy volunteers, as was described in tissue culture (see Heinz A, Jones DW, Mazzanti C, Goldman D, Ragan P, Hommer D, Linnoila M, Weinberger DR: A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biological Psychiatry* 47(7):643-649, April 1, 2000). This finding suggests that this variation in the serotonin transport promoter sequence is a functional variation in humans that leads to a nearly two-fold difference in the expression of the serotonin transporter protein.

Because this variation has been inconsistently associated with the spectrum of anxiety disorders, depression, neuroticism, and fearfulness, it was reasonable to assume that, at the level of brain information processing, this gene may impact the processing of this kind of cognitive information. Again, Dr. Weinberger's group used fMRI to assess the activity of a critical neurosystem in processing emotional information—the response of the human amygdala to perceived danger in the environment. Using a paradigm developed by Ahmad Hariri in Dr. Weinberger's laboratory, the group examined how the amygdala responds to the expression of fear on human faces. The paradigm, which simply asks subjects to match the emotion on a target face to one of two other faces, produces a consistently robust activation of the amygdala in human beings. Because serotonin plays an important role in signaling in the amygdala, the group predicted that serotonin variation in the inherited gene would impact amygdala activity during this kind of exposure and that S allele carriers would show greater neuroticism, anxiety, and similar traits, with greater response in the amygdala to perceived danger, than would L/L- homozygous individuals. And indeed, when two independent cohorts of normal subjects, matched for having no history of anxiety disorders or other traits associated with these genes, IQ, gender, age, and so forth were tested, the results showed that the inheritance of variations in the promoter region of the serotonin transporter gene predicted variations in excitation of the amygdala during the perceptual processing of fearful faces. The S carriers showed a greater amygdala response than L/L-homozygotus individuals, suggesting that individuals with this genotype have exaggerated amygdala excitation during the perceptual processing of fearful stimuli and that this is a likely mechanism for part of what seems to be their relatively excessive fearfulness, neuroticism, and anxiety. This variation of amygdala excitation based on genetic background could also have interesting implications for early imprinting of the fear experience at both the experiential and the molecular levels [see Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR: Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297(5580):400-403, 2002; also available at http://www.sciencemag.org/cgi/content/full/297/5580/400].

Dr. Weinberger said that a third gene of special interest in neuroscience—brain derived neurotrophic factor (BDNF)—has been implicated not just in brain development and the nurturing of critical neuronal systems of special interest to psychiatry but also in influencing the response of brain systems to antidepressant treatment. He said that this gene is certainly critical for learning, memory, and neuroplasticity. Dr. Weinberger reported that his laboratory was very interested in a genetic variation—a non-conservative amino acid substitution in the signal peptide part of the BDNF gene. This is not the mature BDNF protein sequence; rather, it is an upstream part of the sequence in the pro-BDNF molecule that is cleaved after the molecule is transported to its appropriate intracellular location. The signal peptide is rather like a zip code

that the cell uses after ribosomal translation to deposit BDNF in the appropriate place—such as in the dendrite or an axon. Dr. Weinberger's group felt that this non-conservative amino acid substitution would have some impact on BDNF intracellular addressing and trafficking, which might impact BDNF function. The group was very interested in allele variations that functionally impact the gene.

A series of *in vitro* translation and transcription experiments has now demonstrated that this is a highly functional variation that significantly impacts the intracellular trafficking of BDNF. In one experiment at Dr. Bai Lu's laboratory at the National Institute of Child Health and Human Development (NICHD), the group transfected, with viral vectors, hippocampal pyramidal neurons in culture with differential human alleles. The experiment revealed that the *met* allele—the more recent and much-less-frequent mutation—has very abnormal intracellular trafficking—it does not enter dendrites with nearly the same efficiency as the ancestral *val* allele and is not trafficked intracellularly in the same way. Additionally, the regulated secretion of the *met* BDNF allele is reduced considerably in comparison to the regulated secretion of the *val* allele, while constitutive secretion is not changed, and there is no change in the function of the mature BDNF protein with either of these two alleles. These phenomena are consistent with the notion that polymorphism affects the function of the signal sequence. In sum, these results at the basic level would now predict that allele variations should impact the efficacy of BDNF signaling at the level of brain information processing.

BDNF impacts brain development and plasticity in many ways, and the clearest demonstrations of these effects have been in models of plasticity and learning in hippocampal formation. The group used an fMRI paradigm that it had developed to show reliably and consistently an activation response in the human amygdala. The experiment involved subjects in a simple, incidental picture encoding task where the subject was shown scenes and then asked to describe them as representing something "indoors or outdoors." The process of making this judgment involves encoding features of these scenes, and it is thought that the more one completely makes a representation of the features of these scenes, the more the hippocampus is engaged and activates a coherent signal. This kind of incidental processing of scenes consistently activates the human hippocampus. If BDNF has anything to do with the development of hippocampal wiring and the efficiency with which one can engage hippocampal circuitry for incidental processing of experience, one might predict that BDNF contributes to the variance with which such processing is done. However, this variance may reflect factors other than a genetic effect, such as age, alcohol consumption, head injury, and IQ. These other factors also impact the efficacy of hippocampal function and could be confounding factors that contribute variance across the genotype groups. Therefore, carefully selecting and matching subjects is critical to studies that are attempting to isolate a genetic effect.

However, the group did find that a BDNF *met* allele leads to less robust activation of the hippocampus during encoding of incidental scenes. While there is no deficit in the accuracy of individuals reporting whether a scene occurs indoors or outdoors, fewer features seem to be encoded at the neuroprocessing level. The level at which this binding of features takes place also impacts how well individuals can recollect past experiences. In principle, the more individuals bind these features into a representation in the hippocampus and ultimately cross-reference the representations to all prior cortical experiences, the better they should be able to retrieve those

past experiences. To test this assumption, Dr. Weinberger's group performed an experiment to identify voxels in the hippocampus that predict accuracy of recognition and accuracy of recall of past experiences. This region of the brain was interrogated because the group had found that BDNF *met* allele carriers did not remember these scenes later as well as BDNF *val* allele carriers remembered them. The reason for this, Dr. Weinberger said, is that during the encoding process, BDNF *met* allele carriers are not able to recruit a hippocampal response that is as coherent as the response that BDNF *val* allele carriers recruit.

This observation of the relationship between hippocampal function and memory, based on the biology of BDNF, assumes the influence of synaptic architecture of the hippocampus. The overall synaptic activity of the hippocampus can be measured by using a functional neuroimaging tool: NMR proton spectroscopy.

NMR proton spectroscopy can be used to measure the N-acetyl aspartate (NAA) peak—because this is a highly non-specific intraneuronal chemical that rather sensitively tracks the overall oxidative phosphorylation in mitochondria in cells. Thus, it is an indirect surrogate assay of the overall synaptic activity of primarily pyramidal neurons. The assumption is that perhaps the BDNF effect, at the level of cell biology, has something to do with the synaptic architecture of these neurons. When NAA data for a large subject sample—that included healthy volunteers, patients with schizophrenia, and the unaffected siblings of the patients—were examined by Dr. Weinberger's group, the NAA signals in the hippocampal formation showed the predicted relationship between the signal and the BDNF genotype. These results argue that the BDNF val^{66} *met* genotype affects the functional integrity of the hippocampus in human beings. This relationship suggests associations between BDNF and such conditions as bipolar disorder and Alzheimer's disease where the functional integrity of the hippocampus appears to significantly impact the expression of these phenotypes. This effect may be part of the biology in which inheriting this gene may make individuals more likely to express these phenotypes (Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana1 BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, and Weinberger DR: The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell,* in press).

Before concluding, Dr. Weinberger acknowledged the many contributors to the work, including investigators with special expertise in basic molecular science, biology, and the genetics of human brain information processing related to major psychiatric illness. Members of this team include Dr. Michael Egan, Clinical Director of this effort, Dr. Terry Goldberg who was responsible for the neuropsychological aspect of the project and the cognitive testing database; Dr. Bhashkar Kolachana who performed all the genotype studies; Dr. Joseph Callicott, a leader of the fMRI program who conducted the studies of COMT and working memory function; Dr. Venkatta Mattay, another leader of the fMRI project, who performed the amphetamine studies; Dr. Ahmad Hariri, a postdoctoral fellow, who developed and performed the studies on emotional information processing and the encoding task; Dr. Bai Lu's laboratory at NICHD that performed the *in vitro* translation studies with BDNF; and Drs. David Goldman at the National Institute on Alcohol Abuse and Alcoholism and Michael Dean of the National Cancer Institute who assisted with genotype assays and sequencing.

To summarize this presentation on imaging genomics, Dr. Weinberger reiterated two major points. First, genes that are weakly related to psychiatric syndromes are relatively strongly related to the function of neural systems involved in processing cognitive and emotional information in the brain. The elaboration of the molecular effects of genetic variations on these systems should help identify causative and susceptibility mechanisms and new therapeutic targets. Second, approaching the genetics of mental disorders as the genetics of brain information processing is likely to provide us with a new understanding of mental illness that is not based on the descriptive phenomenology that has stymied research in this area for a long time.

Discussion

Dr. Nakamura opened the discussion period by asking whether, with respect to the serotonin reuptake protein, there is an "anxiety gene" or a similar mechanism for describing this phenomenon. Dr. Weinberger replied that many investigators have struggled for years to understand these findings, and they have concluded that there are really no "psychiatric disorder genes." Despite widespread agreement that genetic effects are complex and often small in size, the search for major gene effects continues. However, Dr. Weinberger said the most useful perspective is that there are genes that bias the processing of environmental information so that reactions to that information are more extreme, which is the assumption with respect to the serotonin reuptake protein. One reason for the interest in facial-processing paradigms is that the human brain pathway that processes facial emotion is one of the first brain pathways to develop, at least functionally, during the first 3 months of an infant's life, when studying the mother's face is the infant's major preoccupation. The first expression of emotion in a human infant is based on an emotion on the mother's face. This critical organization of synaptic space and connectivity based upon the environmental stimuli that impinges on these pathways has a lifelong impact on how the amygdala responds to this kind of information.

It is possible to imagine that, if one has a system that is constructed a little differently with regard to how information impacts the amygdala, then there is a genetic "bottleneck" in the adaptive possibilities of one's system. However, there may be genes that are protective or that compensate or that make this genetic bottleneck irrelevant. Thus, it is necessary to begin to build a genetic architecture in order to understand how these genes interact.

In sum, Dr. Weinberger said there is an anxiety disorder gene but only in the sense that having an anxiety disorder is all about susceptibility, bias, predisposition, or likelihood. Thus, in that sense, there is an anxiety gene, but other factors are necessary for a manifestation of the disorder—such as an anxiety attack—to result.

Dr. Henry Lester, commenting that each new level of imaging resolution seems to expedite groundbreaking discoveries in neuroscience, asked whether the magnetoencephalography (MEG) machine is likely to show that the effects of these genes are actually limited to one set of neurons or one set of synapses. In reply, Dr. Weinberger said that Dr. Richard Coppola, Director of NIH's MEG Core Facility, argues that genes work in a time domain where there is no information processing; in other words, genes do not affect moment-to-moment information procession but rather produce ripple effects across summed experiences. Dr. Weinberger said

that this phenomenon illustrates how remarkable it is that these signals can be demonstrated at all. This concept of examining how genes work is similar to the concept of how PET worked in its early days—as signal detection, not necessarily resolution. It is also similar to the concept of radar, which has very limited intrinsic resolution but can be very sensitive to signal detection because repeated sampling within subjects and controlling for many other confounds allow the extraction of signals that seem to relate to the unique identifier of samples—genes. It is assumed that, at the level of brain information processing, the time domain is much faster than that of PET or radar. Actually, Dr. Coppola and Dr. Georg Winterer have been leading studies using EEG signals to examine electrophysiological evoked potential signals. The assumption is that there will be more incisive system neuronal phenotypes that can be identified using techniques such as MEG that will provide a stronger biological signal of genetic effects.

After complimenting Dr. Weinberger on his synthesis of two of the most powerful methodologies for elucidating human neurobiology, Dr. Jeffrey Lieberman asked whether the magnitude of the variance accounted for by the different polymorphisms across the three genes he discussed is similar or significantly variant. Dr. Weinberger explained that this was a difficult question to answer because the paradigms vary. The strength of the gene effect depends, to some extent, on how much variance other factors contribute to the signals.

Elaborating on his question, Dr. Lieberman said that one could envision that susceptibility alleles might contribute in some additive manner—a cumulative risk approaching a threshold—or that there are other mechanisms acting synergistically. For example, a recent study examining the genes expressed in the 22Q11 haplo-insufficiency model found that all 15 of the major genes in that region are co-expressed in a common group of tissues, suggesting that some cumulative effect may be contributing to the phenotype of that syndrome. Dr. Weinberger reiterated that the components of this pathway produce a wide array of psychiatric syndromes. Many emerging concepts of how genes contribute to mental illness may be over-simplifications. The struggle to understand how genes contribute risk for mental illness, in his view, is an attempt to understand how they contribute variance to brain functioning. To date, the struggle has not been in making the associations; rather, efforts have focused on replicating effects and determining the strength of the effects. Moving to the next level will require understanding the effects of genes specifically on the type of information processing deemed most relevant. Most likely, there will be many interacting gene effects on a variety of these processes rather than specific genes for subtle variations in how people relate to their environment. There are many other systems in the brain that are affected by genes that look like the schizophrenia susceptibility genes that Dr. Weinberger talked about. Moreover, the effect sizes and odds ratios for a single gene are always very small and pertain to general human populations. For example, no relationship has been found between the BDNF genotype and schizophrenia, although it has been associated with bipolar disorder. This lack of relationship does not mean that BDNF has no impact on schizophrenia—because it does seem to impact the hippocampus—but that no relationship has been found in the general population of people with a diagnosis of schizophrenia. In an epistatic model where subjects' genetic backgrounds are defined by other inheritances, the BDNF effect might become very important for explaining variance in individuals, for example, with a COMT *val* allele in addition to other genetic irregularities. That will be the next level for exploration.

Dr. James McClelland lauded the excellence of the behavioral paradigms as well as the genetics and imaging research in the work done by Dr. Weinberger's laboratory. Following up on the behavioral implications of the work, Dr. McClelland asked how an illness that is as supposedly heritable as schizophrenia could be manifested, as the concept of small susceptibilities having an additive impact seems implausible. Dr. Weinberger replied that the involvement of as few as six genes interacting multiplicatively could support the belief that 60 percent of the population liability for schizophrenia is genetic. However, he opined, these are probably not the same six genes in all populations. The field has been stymied by the belief that everyone with the same illness has the same genotype. It is too easy to forget what heterogeneity really means—which is that a number of genes are likely to contribute to variation in biological functions, and, depending upon the size of the biological effect or how it interacts with other genes, the six genes that contribute to one group of families or a population could be very different from another six genes that interact multiplicatively to explain genetic liability for another population. There probably will not be an unlimited number of genes; there may be as many as 20. Essentially, genes are a kind of biological toolbox that an individual uses to negotiate the environment, although other factors also influence outcomes. So, theoretically, any of these genes produce molecular "bottlenecks" in how systems adapt to the environment.

Dr. Weinberger went on to explain the goals for his work in examining genetic associations with brain systems via imaging studies. The first is to get a better understanding of causation mechanisms. The second is to improve the conceptualization of diagnosis and the meaning of variability in the expression of different syndromes. It may turn out that non-biological or non-genetic factors, rather than biological backgrounds, account for variation in outcome. The third reason is to assist in finding new therapeutic targets based on molecular dissection in animal models and in human tissues and the discovery of genotypes for expression profiling, where the search for molecular manifestations of the effects is looked for, based on the genotype of the tissue. This approach to ascertaining how genotype determines the adaptation that cells make over a lifetime opens up dramatic new approaches to finding pathways that might be able to be interacted with therapeutically.

When Dr. Megan Gunnar questioned whether attention also is being given to understanding the developmental potential of gene activity, given the new understanding of adult regulation in the expression and activity of these genes, Dr. Weinberger agreed that this should be encouraged and noted that Dr. Cynthia Shannon-Weickert in his lab has been working to initiate such studies.

Dr. Charles Nemeroff commented that the genotyping work in relation to brain functions that Dr. Weinberger is conducting likely will make its biggest contribution by providing enriched samples for clinical studies. His findings already explain much of the variance in response to amphetamine and to SSRIs that has not heretofore been understood. No studies to date have examined the multiple polymorphisms of the transporter in relation to treatment response, and these studies need to be done. Thus, the work of Dr. Weinberger's lab opens up an entire field. Dr. Nemeroff asked Dr. Weinberger if there is convincing evidence that N-acetylaspartate (NAA) is a marker of synaptic activity rather than of integrity. Dr. Weinberger replied that no distinction was made between them. He said that, while a neuron that is under attack probably has less synaptic activity, NAA is only a surrogate measure, and Dr. Nemeroff's point was well taken.

Dr. Ming Tsuang noted that this presentation set the stage for future developments and that the next task will be to use the findings to prevent schizophrenia, manic depression, and other mental illnesses by developing a diagnostic test to discover the premorbid state of these illnesses. An immediate task is to develop a diagnostic test that will identify and characterize the protein structure for a subgroup of persons at risk for schizophrenia or anxiety disorder or other psychiatric disorders. The NIMH's IRP, he stressed, should take the lead in developing such a diagnostic test for the premorbid state that can be utilized in prevention.

Echoing the compliments for the excellent presentation, Dr. Eric Nestler observed that the field still does not generally accept the notion that there are no psychiatric disease genes. While the genetic variants studied by Dr. Weinberger can explain some normal behavioral variations, it still may be possible that "big" genes cause mental illnesses. Agreeing that the APOE4 gene effect in Alzheimer's disease is a model effect, Dr. Weinberger explained that it is not, in fact, a risk gene for Alzheimer's disease. Rather, APOE4 is a gene that affects the trafficking of lipids and, to the extent that this effect influences the emergence of Alzheimer's pathology, it increases the risk for Alzheimer's disease. However, APOE4 also increases risk for atherosclerotic heart disease, for Lewy Body dementia, and for many other illnesses. In his opinion, Dr. Weinberger continued, all of the "psychiatric genes" will turn out to be these kinds of gene effects. To the extent that they have relevance for the emergence of problems associated with psychiatric illnesses, they are in the realm of psychiatric risk genes.

NIMH UPDATES

Clinical Trials Workgroup

Dr. Jeffrey A. Lieberman, Professor and Vice Chairman of the Department of Psychiatry at the University of North Carolina in Chapel Hill, gave a preliminary report on the work of Council's Clinical Trials Workgroup. The Workgroup was charged with reviewing the portfolio of clinical treatment studies, primarily supported in the Division of Services and Interventions Research (DSIR) through the grant mechanism. This review will include an assessment of the balance, quality, comprehensiveness, attention to specific disease entities, and any critical knowledge gaps, deficiencies, or redundancies among the funded studies—all in the context of addressing public mental health priorities. In addition, the Workgroup will consider whether available funding mechanisms are appropriately used and whether supported studies bridge the full range of treatment development research—from treatment development, to classical clinical trials, to more naturalistic or quasi-naturalistic effectiveness trials—to the delivery of mental health services. The goal of the Workgroup's portfolio review is not only to identify critical knowledge gaps or areas of need and opportunity but also, where necessary, to make recommendations about how these could be better or newly addressed. The Workgroup also is charged with assessing whether funded projects are progressing as anticipated and delivering promised data and other products in a timely fashion and recommending to Council mechanisms that might be used by NIMH staff to monitor funded projects' performance on an ongoing basis.

The members of Workgroup include scientific and public representatives from Council and investigators from the extramural community, who bring to this evaluative process a broad range of expertise and perspectives. Thus far, the Workgroup has held a series of teleconferences to define and understand the tasks and to determine a work plan. An in-person meeting is set for October at NIMH, when program staff members will describe their research portfolios and the Workgroup will begin mapping these projects to public mental health needs as they are currently understood (and which will be updated when Dr. Ronald Kessler, Professor of Health Care Policy at Harvard University Medical School, reports on his new epidemiological data).

Discussion

After Dr. Nakamura acknowledged the work that Drs. Grayson Norquist and William Harlan have provided in staffing this Workgroup, Dr. Lester asked how the special topic of long-term longitudinal studies fit into the context of clinical trials. Dr. Lieberman responded that one of the specific goals of the Workgroup's review is to facilitate the conduct of longer-term trials. To date, this is being accomplished through a series of contract awards that are bridging the gap between pharmaceutical industry-sponsored regulatory trials and the initiation of effectiveness studies, the management of which extends across NIMH. Dr. Nakamura added that this issue has been raised previously and will be addressed in similar and planned portfolio reviews for all three funding divisions. The Workgroup was asked to focus initially on DSIR's portfolio rather than attempting to take on the whole of NIMH.

NIH DIRECTOR'S REPORT

Dr. Elias A. Zerhouni, Director, National Institutes of Health, expressed his pleasure in attending this Council meeting to make a major announcement that fulfills one of his most important priorities—finding and recruiting the best and brightest scientific leadership for NIH. Whereupon, he introduced Dr. Thomas Insel as the next Director of NIMH and explained the thorough search process that was conducted, including a personal visit with Dr. Insel and other candidates. Because NIMH has such a prestigious reputation, many outstanding scientists throughout the country were interested in this directorship. However, Dr. Zerhouni reported his visit with Dr. Insel in Atlanta convinced him that Dr. Insel would be an outstanding leader for NIMH. Mental health research, Dr. Zerhouni said, is a critically important area of activity at NIH. There are implications in terms of the mission of NIMH that are far beyond anyone's grasp in terms of both national health and the future of the Nation. In that regard, Dr. Zerhouni said, we need to be as proactive as possible. He said that, although the field has been challenged by the difficulty in classifying disease—having objective markers of disease—much progress has been made in that regard and will continue to be made. One of the qualities of Dr. Insel that Dr. Zerhouni finds attractive is Dr. Insel's compelling vision for the field of mental health research and his understanding of its many challenges and opportunities.

Dr. Zerhouni noted that Dr. Insel has shown outstanding leadership in shaping research. He began his research career as a clinical associate in NIMH's Clinical Neuropharmacology Branch in the Intramural Research Program (IRP) in 1979. After 15 years at NIMH in various administrative and research positions, he was appointed Professor of Psychiatry at Emory University in Atlanta and Director of the Yerkes Regional Primate Research Center, which he developed into a premier facility. Dr. Insel currently serves as a founding Director of the Center

for Behavioral Neuroscience, funded by the National Science Foundation (NSF). As Director, he helped establish an interdisciplinary consortium for research and education among eight Atlanta colleges and universities. This Center was one of five selected for funding by NSF from a field of 400 respondents to the announcement and 283 competing applications. Dr. Zerhouni commended Dr. Insel for his outstanding scientific record, his novel approach to the conduct of neurobehavioral research, and his valuable team-building and leadership skills.

COMMENTS BY THOMAS A. INSEL, M.D.

After acknowledging the gracious introduction, Dr. Insel, the newly appointed NIMH Director, spoke briefly of the honor and privilege afforded by the position and his eagerness to work with Dr. Zerhouni and others at NIH. He also noted the propitious timing of his appointment at the end of a 5-year funding cycle for NIH when its research budget doubled and accountability for the investment is paramount. He indicated his plan to demonstrate the wisdom and worthiness of this research commitment by working with Dr. Zerhouni and others at NIH, particularly NIMH staff and grantees. NIMH has a special obligation to keep the public trust, Dr. Insel said, by providing complete information about research progress and accomplishments.

Commenting on the changes taking place at NIMH and the outstanding leadership that this institution had enjoyed, Dr. Insel noted that Dr. Steven Hyman, during his 5-year tenure as Director, revitalized the intramural program, reorganized the extramural program, and provided outstanding scientific leadership. Dr. Hyman was aided in these accomplishments by excellent staff, including his Deputy Director, Dr. Nakamura.

Dr. Insel noted that Dr. Nakamura had provided outstanding leadership for NIMH during the last 10 months while serving as Acting Director and that his steady hand and good judgment and insight had been beneficial for everyone.

Dr. Insel said that he first joined NIMH in 1979 as a clinical associate in the Clinical Neuropharmacology Branch under the directorship of Dr. Dennis Murphy and went on to hold several administrative and leadership posts. During many of his 15 years at NIMH, he worked in the clinical arena, first running an inpatient unit and then specializing in clinical research on anxiety disorders and depression, with a focus on obsessive-compulsive disorder (OCD), then described as "obsessive-compulsive neurosis." He was part of a research group that initiated some of the first treatment trials for OCD in the United States using serotonin reuptake inhibitors. Over time, he became more interested in the basis of behavior and affect—how genes affect cells, and how cells affect systems, and how systems, in turn, create normal or abnormal behavior. This interest led to an opportunity to develop a laboratory that focused on social neuroscience—trying to identify the cells, genes, and molecules that were important systems components for social information processing, social attachment, parental behavior, and other complex aspects of behavior.

About 8 years ago, Dr. Insel reported, he was recruited by Emory University to direct the Primate Center, where most of his work focused on developing a program in HIV vaccines. In the last 3 years, he has been more involved in issues pertaining to minority recruitment and diversity in science through his work with an NSF-funded center. The center focuses on the

neurobiology of social behavior and increasing the participation of under-represented minorities in science at the undergraduate, graduate, and postdoctoral levels and on faculties.

Dr. Insel summarized his research interests as clinical research, aspects of neuroscience at the molecular and cellular levels, and building programs that move the whole field forward in areas that are relevant to mental health, particularly minority recruitment and HIV. Dr. Insel indicated his expectation to listen to a broad range of people representing both the advocacy and scientific communities and to meet with staff members of the Institute's intramural and extramural programs. The next few years are going to be very important, concluded Dr. Insel, and he looked forward to working with all those present and receiving their input and guidance.

Discussion

Following Dr. Insel's remarks, Dr. Zerhouni reiterated his praise for Dr. Insel's vision, problem-solving skills, and leadership capabilities, particularly for consensus-building. He also commended Dr. Nakamura for his leadership, dedication, and skill in serving as the Acting Director of NIMH. Dr. Zerhouni said that, in the next 5 years, NIH will face great challenges. On one hand, the period of budget doubling is ending, and questions are being asked about how propitiously these resources are being managed. On the other hand, Dr. Zerhouni noted that the research opportunities have never been better for all of the institutes, with the convergence of science in the genomics and post-genomics era and the need to increase the quality of the data density through both pure biological research and computational approaches to biological systems. Proactive visionary leaders are needed at NIH to direct innovative and high-quality biomedical research programs that address public health priorities. Council members, he noted, have a vital role in promoting research, and he encouraged more cross-institute Council communications to develop and implement new strategic research initiatives.

Dr. Nakamura acknowledged the strong scientific leadership provided by Dr. Zerhouni, an Algerian immigrant who serves as a prime example of how individuals from different countries have contributed to the United States. After coming to the United States, having earned his medical degree at the University of Algiers School of Medicine in 1975, Dr. Zerhouni embarked on a research career in radiology and has made vital contributions to the refining of neuroimaging and the techniques that are being used today to create breakthroughs in the understanding of human behavior through genetics, as Dr. Weinberger illustrated here earlier. Dr. Zerhouni most recently was Executive Vice Dean of The Johns Hopkins University School of Medicine, Chair of the Department of Radiology and Radiological Science, and Professor of Radiology and Biomedical Engineering—positions requiring his strong leadership and team-building skills. His ability to perform research and administrative functions was a testimony to his remarkable breadth of vision. Dr. Nakamura concluded by noting that Dr. Zerhouni's understanding of the management of science positions him well to provide strong leadership to NIH.

Dr. Charles Nemeroff, Reunette W. Harris Professor and Chair, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, commended Dr. Zerhouni's selection of Dr. Insel as the next NIMH Director and added that Dr. Insel is the epitome of

courage defined as grace under pressure. Dr. Nemeroff added that Dr. Insel will leave his current position as a most beloved professor, a respected scientist, and a great person.

Dr. Wilson commented that his appointment to Council soon would be ending and that he wanted to express his personal concerns about health disparities. Symbolic of health disparities are the many communities that have become disaffected with scientific inquiry and have not yet been convinced by NIMH outreach activities to participate as subjects in research investigations. Outreach activities are particularly important for service providers and policymakers as they have the responsibility for translating scientific inquiry into real-life outcomes. Acknowledging these important concerns, Dr. Insel reiterated his belief that bridging science and service is a major commitment of NIMH. Although the Institute focuses on research, it also is critical to strengthen its bridges to relevant agencies, such as SAMHSA, and to make certain that research discoveries are translated into practical applications. He commented that many frontline treatment providers may not fully appreciate the effectiveness of available mental health treatments, which are comparable with those in many other areas of medicine. The challenge remains to better understand and close the gaps in applying important research findings to the changing environment of health care delivery. Dr. Insel referenced the recent "NIMH Five-Year Strategic Plan for Reducing Health Disparities" (see http://www.nimh.nih.gov/council/-diversity.pdf) as an exemplary document that can serve as a master plan for resolving some of those issues.

Dr. Tsuang commended staff members at NIMH for their compassion and helpfulness in assisting researchers and others in an effort to build a robust program of research. He also applauded Dr. Nakamura's willingness to serve as NIMH Acting Director, saying it was rare to find someone who offered such solid support.

Dr. Squire asked Dr. Insel if it would be possible, under his leadership at NIMH, to have open and frank discussions about the controversial issue of stem cell research in an effort to bring more science into the discussions. Noting that NIH has some extraordinary stem cell researchers who are working with mental health investigators, Dr. Insel replied that this topic seemed appropriate for a future Council meeting.

Ms. Gail Hutchings, the newly appointed Acting Director of CMHS, offered to Dr. Insel her congratulations and a warm welcome on behalf of SAMHSA and CMHS, pledging her commitment to work with NIMH to improve the delivery of effective mental health services to all Americans. She added that the President's New Freedom Commission on Mental Health is a once-in-a-generation opportunity for CMHS and NIMH to participate in the development of a report that will assess the current U.S. mental health service delivery system and recommend improvements. This activity will provide agencies, such as CMHS and NIMH, an opportunity to address the strengths and weaknesses of the mental health system as described in the report and, importantly, to carry out many of the Commission's recommendations. Anticipating that the partnership between CMHS and NIMH that flourished under the leadership of Dr. Nakamura would continue under Dr. Insel, Dr. Hutchings looked forward to the opportunity to consider new directions in translational work. Dr. Insel responded that he welcomed the opportunity for ongoing collaboration with CMHS and SAMHSA and that he looked forward to the Commission's report.

NIMH UPDATES

Mental Health Research After September 11

Dr. Farris Tuma, Chief of the Traumatic Stress Program in the Developmental Psychopathology and Prevention Research Branch, DMDBA, said that the sadness, grief, anxiety, and depression that many experienced and that some are still experiencing in response to the September 11 terrorist attacks on the United States underscored the need for improving mental health services for those coping with mass violence and disasters. NIMH has provided much information to help people understand and address the responses to the September 11 attacks. There also have been several NIMH initiatives to better address those responses, which Dr. Tuma said that he and Dr. Ritchie would briefly review. New research activities have begun under 10 new Rapid Assessment Post Impact of Disaster (RAPID) grants and 9 supplements to ongoing studies. In addition, the NIMH Traumatic Stress Program has been working with SAMHSA and the HHS Secretary's Workgroup on Disaster Mental Health to optimize the public health system's response capability. To address some unresolved needs in response capability, Dr. Tuma said that he and Dr. Ritchie would propose a concept for Council's approval that will encourage prospective, systematic research on mass violence and disasters.

An NIMH news release (see http://www.nimh.nih.gov/events/prrapidgrants.cfm) describes multiple projects that NIMH initiated after September 11 in response to the events of that day. Additionally, new collaborations have been established among the intramural research programs and extramural investigators that specifically focus on the mental health consequences of the anthrax episodes and responses to ongoing threats in the Washington metropolitan area and elsewhere. The goals of these research projects complement the Institute's overall portfolio and mission in terms of reducing the burden of mental illness. Relevant work is underway in all three of NIMH's extramural research divisions (DNBBS, DMDBA, and DSIR) and in the intramural program. The focus is on improving the understanding of the impact of trauma, violence, and victimization on mental health and on gaining insights through basic, behavioral, epidemiological, clinical interventions, and services research. Nearly four decades of research in these areas at NIMH has paid off in some remarkable accomplishments—most notably, greater insights into brain and behavioral changes associated with trauma that have been used to inform treatments, many of which are more effective than commonly recognized, as Dr. Insel noted. Moreover, basic research is providing clues for promising approaches to preventing disorders like posttraumatic stress disorder (PTSD).

Dr. Tuma then reported on recent activities reflecting NIMH's role since September 11 as a broker between mental health experts on disaster and trauma and a variety of Federal, State, and local health and mental health agencies and care providers who have requested assistance.

- The NIMH Traumatic Stress Program is an active participant in the HHS Secretary's Workgroup on Disaster Mental Health and has strengthened linkages with SAMHSA to try to place research findings directly into the process for planning and responding to national disasters.
- The NIMH Traumatic Stress Program has joined with SAMHSA to co-sponsor an upcoming Institute of Medicine panel and report on responding to the psychological consequences of

terrorism that will focus on optimizing the public health system's response capability.

- Under the direction of Dr. Regina Dolan-Sewell, NIMH is co-sponsoring a meeting with the Center for Urban Bioethics at the New York Academy of Medicine to address, among other topics, ethical issues pertaining to the design and implementation of post-disaster research. Participants reflecting a broad range of perspectives will include researchers who work in this area, ethicists, survivors, representatives from community organizations, clinicians, and institutional review board (IRB) members. The goal is to provide guidance for trauma and disaster research to move forward in a constructive and appropriate manner.
- Earlier this year, NIMH organized a workshop on the relationship of acute trauma responses to psychopathology that attempted to identify important predictor variables that should be measured post-trauma (e.g., biological, psychological, and behavioral aspects) in order to specify populations, analyses, and designs to include in studies that will inform the NIMH agenda with respect to diagnosis and evaluation of acute reactions, risk factors for pathology, and prevention or early intervention activities. The workshop also attempted to identify treatment and prevention approaches to trauma that need further development.
- NIMH collaborated with the Departments of Defense, Justice, and Veterans Affairs, and the American Red Cross to organize and disseminate guidance on what is known about early mental health intervention after large-scale trauma.

Dr. E. Cameron Ritchie, Program Director for Mental Health Policy and Women's Issues in the Office of the Assistant Secretary of Defense for Health Affairs, provided additional information about this multi-agency workshop on mental health and mass violence that was organized to address the impact of early psychological interventions and to provide guidance on evidence-based best practices in this area. The proceedings of the conference can be accessed through the NIMH Web site at http://www.nimh.nih.gov/events/prmassviolence.cfm.

A team of representatives from the Health Affairs section of the Department of Defense, the Office of Victims of Crime in the Department of Justice, the National Center for Post-Traumatic Stress Disorder in the Department of Veterans Affairs, NIMH, SAMHSA, the American Red Cross, and consultants to the Surgeon General were assembled, along with subject matter experts from five countries and the United States. These experts included Drs. Arieh Shalev from Israel, Richard Bryant and Beverly Raphael from Australia, and Simon Wessely from England. Special tribute was also paid to Dr. Richard Wyatt from NIMH, who passed away this summer, for his help in planning this effort.

The critical issues under consideration pertained to the elements of good practice; key operating principles; the best timing for interventions; appropriate screening mechanisms for ascertaining who really needs a debriefing or another intervention; the timing and procedures for follow-up; the expertise, skills, and training needed by providers; and the type of data that should be collected and the methods that should be used for that data collection. Ethical issues surrounding the design and conduct of disaster research were another area of discussion.

The Workgroup identified six descriptive variables that should be considered in providing assistance post-trauma: (1) What type of disaster is it—natural or man-made, anticipated or totally unexpected? (2) What population is affected—first responders, military personnel, family and community members, or strangers? (3) What is the post-trauma environment—totally

devastated, uninhabitable and filled with toxins, or safe enough to move about in freely? (4) Is the timing of the disaster response very slow or fast? (5) Is the responder someone from the community who is also affected or an outsider? (6) What type of intervention is applied?

Under the guidance of the international experts, the conference participants conducted a literature review that rated published reports on a continuum according to six levels of evidence—ranging from randomized clinical trials (RCTs) to well-designed but non-randomized cohort or case control analytic studies to naturalistic or multiple time series studies to consensus-based agreement on best practices to recently developed treatments that have not been empirically tested. It quickly became apparent that few RCTs have been conducted in this field; most publications comprise anecdotal reports of success. This examination of the relevant literature was deemed appropriate because every disaster over the past 10 years has attracted teams of well-intentioned mental health professionals who wanted to help survivors by conducting debriefings, although published evidence regarding the effectiveness of debriefings remains controversial.

The first focus should be on security, safety, and survival. Survivors will not want to discuss the experience or talk about feelings until they know that their children and relatives are safe and that they have food and shelter. The continuing safety of the environment also needs to be assessed. Psychological first aid comes next, entailing support for the distressed, reuniting families, fostering communications, protecting against further harm, and providing important information about continuing risks. Monitoring the recovery environment is critical to any relief efforts. This can be accomplished by close observation of the victims, constantly checking for toxins that can have long-term physiological effects, being sensitive to previous or ongoing threats, assessing the services that are being delivered, and watching the media reports. Psychological help and other forms of assistance may come from a variety of sources such as local leaders and disaster relief teams. Any help should be based on a needs assessment of group as well as individual needs.

Disaster assistance can be provided in many ways. After the Pentagon was attacked on September 11, much therapy was delivered by providers who "walked around" and were visible and accessible. Active outreach is absolutely necessary to reach most people. While this can be accomplished through established community structures, it can be enhanced through flyers, Web sites, and media interviews. Mental health experts also can assist in providing technical assistance, consultation, and training to local leaders.

Another important component of disaster assistance is fostering resilience and recovery. Dr. Ritchie reflected that much of the work she did at the Pentagon post-September 11 was aimed at reuniting the workplace—getting traumatized people to stop working 14 to 16 hours a day and to reach out to each other. She organized potluck suppers and encouraged people to get together and share experiences about what happened. Survivors also need to be educated about the stress response, triaged according to their assessed response patterns, and referred for mental health clinical interventions if they continue to experience coping difficulties.

The formal workshop report contains guidance on specific "best practices." Among the most important findings are the following:

- Early, brief, and focused psychotherapeutic intervention can help reduce distress, especially among bereaved spouses, parents, and children.
- Cognitive behavioral therapy has the most evidence-based utility for reducing the incidence, duration, and severity of acute stress disorder, PTSD, and depression in survivors.
- It does not appear that classical one-on-one debriefing (i.e., a recital of thoughts and emotions evoked by the traumatic event) reduces the risk of subsequent PTSD or related adjustment difficulties and may actually cause harm—particularly if the trauma was especially horrific. One problem with this approach is the frequent lack of any follow-up capability.
- Other popular practices (e.g., eye movement desensitization reprocessing, or EMDR) have not been proven effective as a preventive intervention.

Although more research about effective mental health responses to mass violence and disasters is desperately needed, this remains a challenging area. Appropriate research should be planned in advance because IRB approvals are not readily available on short notice following a disaster. Protocols must be readily implementable—using well-qualified experts who have obtained permission with informed consent procedures in advance, established contacts with reputable caregivers, and developed mechanisms for collaborating with authorities and using a standard taxonomy.

Dr. Ritchie reported that the remaining research questions that need addressing are: what are the most significant psychological and biological variables to monitor in the post-event environment; what different subgroups are represented in the affected population (e.g., previously traumatized victims appear to be more vulnerable than others); what are appropriate mental health interventions; who are appropriate providers; and, relatedly, whether a different mechanism is required to support this type of research. While the NIMH RAPID grant seems to be a good first step, additional means of support may be required.

Concept Clearance: Disaster Mental Health Research, Education, and Rapid Response

Dr. Tuma explained a concept that NIMH is considering in order to encourage prospective and systematic research pertaining to mass violence and disasters. Such research is necessary to better understand and respond appropriately to disaster survivors and victims of other traumatic events, including terrorism. Because these acts of mass violence are a frightening reality with the potential to cause great economic, physical, and psychological harm, there is a pressing need to learn more about the biological and behavioral consequences of traumatic stress experienced by disaster-exposed groups. The ability to generalize about the effects of disasters has, to date, been limited by large differences in the conceptualizations and methodologies used by a wide range of clinicians and behavioral scientists.

There are numerous challenges to improving research in this area by developing the capacity for rapid data collection in the immediate aftermath of mass violence, enhancing the quality of the studies, and incorporating new knowledge about the neurobiological nature, cause, pathogenesis,

treatment, and prevention of posttraumatic psychopathology. The general goal is to facilitate competitive programs for mental health research, education, and rapid response that would involve the very best investigators working with the agencies and services brought together at the workshop described by Dr. Ritchie. Applications would be solicited from teams of national and local mental health researchers, planners, and providers with special interest and expertise in disasters and mass violence. The focus of such applications would be on:

- Developing and conducting training about state-of-the-art disaster mental health research methods
- Refining assessment and measurement methodologies
- Developing protocols for rapid data collection efforts following major disasters and acts of mass violence in conjunction with Federal, State, and local stakeholders

It is imperative to gain a better understanding about the helpfulness or potential harm caused by media communications about risk and other health-related behavior as well as helpfulness or potential harm caused by large-scale public mental health interventions following disasters. While the RAPID research grant mechanism has proved useful for putting pilot projects in the field in a 6- to 8-week timeframe, the proposed concept would be more comprehensive in facilitating coordination across the limited existing expertise of the entities responsible for organizing and delivering care.

Discussion

When Dr. Nakamura opened the discussion of this proposed concept, Dr. Durham expressed hope that the potential contribution of the private sector to the proposed research activities would not be overlooked. Dr. Durham estimated that her colleagues who work on these issues at United Health Care, Kaiser Permanente, Blue Cross/Blue Shield and a number of other smaller healthcare organizations are collectively responsible for more than 20 million covered lives. All of these organizations have varying levels of sophistication and databases that range from those in laboratories to diagnostic databases that can track the natural history of disaster responses. Laboratory databases can be used for Centers for Disease Control and Prevention (CDC)-style surveillance activities to alert the community about an anthrax outbreak or other toxic exposure.

After agreeing that the private sector should not be overlooked, Dr. Nakamura asked for a motion to approve the concept. This was duly made, seconded, and approved by a show of hands without further discussion.

Treatment Development Workgroup

Dr. Wayne Fenton, Acting Deputy Director of NIMH, updated Council on the recent activities of the Institute's treatment development initiative, which essentially is designed to enhance the transition from the type of brilliant scientific research presented by Dr. Weinberger into developing better treatment for patients with psychiatric illnesses. At the request of Council, the Treatment Development Workgroup was formed last May to review the Institute's involvement in treatment development activities and to identify areas where NIMH can complement and enhance industry efforts to develop better treatments for mental illnesses. The participants in

this effort include representatives from academia and industry with expertise in clinical issues, psychometrics, psychology, behavioral science, basic neuropharmacology, and genetics.

Reviewing the rationale for the Workgroup, Dr. Fenton noted that even the best available treatments have limitations. In clinical trials of antidepressants, although many patients respond to acute treatment, significant medication side effects and residual symptoms are typical, often contributing to chronic depression and a high risk of relapse. Similarly, current treatments for schizophrenia, while vastly better than those of 10 years ago, provide only partial relief (e.g., only one in five patients recovers sufficiently to return to work), and most individuals who have a first episode of schizophrenia will also experience a second episode.

A major reason for the lack of further progress in the development of therapeutics, in the Workgroup's view, is a singular focus by psychopharmacologists on only certain molecular and clinical targets. Almost all of the medications used today are based on the mechanisms of action of primarily monoamine receptors and their re-update proteins. Valid new pathophysiologically relevant molecular targets are sorely needed. It is not uncommon for several very similar compounds marketed to be for a particular problem, as is the case with the SSRI antidepressants. In addition, psychopharmacologists have focused on the same clinical targets. Most current pharmacologic agents broadly target DSM-defined diagnostic categories such as depression, schizophrenia, or PTSD; however, rather than treating diagnostic entities, they treat dimensions of dysfunction and dimensions of symptoms that cut across diagnostic entities. Thus, an antidepressant may treat a patient's depressed affect, whether it occurs in schizophrenia, major depression, or other illnesses. Because the new drug approval process of the Food and Drug Administration (FDA) generally considers global DSM diagnoses rather than syndromes as legitimate targets for drug registrations, the pharmaceutical industry has focused drug development accordingly—although pain and fever are notable exceptions.

While the FDA has no fundamental objection to looking at syndrome-based clinical targets, such as fever and pain, the agency has indicated that it will not accept a new clinical endpoint for the convenience of any single drug company. The FDA has encouraged NIMH to use its convening authority to bring together industry, academia, and regulatory agencies to define new clinical target, methods, and measures to assess efficacy for drug registration.

It is important to distinguish what contributions private industry can best make and what competencies are best left to the government. The private sector excels in such activities as refining existing mechanisms, combinatorial chemistry, screening of new compounds, and pre-clinical toxicological or kinetic development. By contrast, the Institute could best assume responsibility for supporting basic scientific research studies that focus on pathyphysiology, help to identify phenotypes, and identify new molecular targets for drug development. Additionally, NIMH could use its convening authority to examine dimensions of psychopathology that may be closer to pathophysiology and more amenable to the influence of pharmacologic agents and to conduct proof-of-concept trials followed by effectiveness studies.

The NIMH treatment development initiative has focused on two priorities over the past 6 months: a contract (NIMH-02-DM-0006) for treatment development studies for cognition in schizophrenia, which was recently awarded to the University of California, Los Angeles, and a

Request for Applications (RFA), MH03-002 "Development of Tools for the Assessment of Depression," which was recently published (see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-03-002.html).

Reviewing the rationale for focusing on cognition and schizophrenia, Dr. Fenton pointed out that cognitive deficits in schizophrenia are more strongly correlated with functional impairment than other syndromal dimensions of this disorder (i.e., delusions, hallucinations, anhedonia, blunted affect, and disorganization). Yet most current antipsychotic medications were screened against delusions and hallucinations; they are relatively successful in treating those symptoms but not in alleviating cognitive problems. Basic science has made real progress in understanding the importance of cognition as it relates to schizophrenia and other illnesses. Spanning the gap between such progress and its translation into clinical applications is the goal of the treatment development initiative.

Showing a slide listing six putative neurochemical modulators that may have translational relevance for studies of cognition in schizophrenia, Dr. Fenton described two of these models in more detail. The first model is of prepulse inhibition (PPI), or the cognitive ability to adapt to and screen out stimuli, such as the potentially distracting sound of a jackhammer in a parking lot, so that one can think and move forward. In PPI experiments, the pulse consists of a loud noise, and a startle response is measured, either physically or on as evoked potentials in an EEG. In essence, in normal controls, if a warning is provided before the loud noise, a gating process inhibits the response. But patients with schizophrenia are significantly less able than normal controls to have this PPI response. However, Council liaison member Dr. Robert Freedman and others have discovered that nicotinic agonists can transiently normalize deficient PPIs in animal models. Clinically, patients with schizophrenia may smoke cigarettes in self-medicating attempts to transiently attenuate the cognitive deficits associated with their disorder. Unfortunately, as nicotine rapidly desensitizes receptors, it has little potential value as a treatment. However, it may be possible to develop a nicotinic agonist that will not rapidly desensitize receptors and thus normalize this schizophrenia-associated cognitive deficit over a longer period of time. This is the type of movement from basic research into treatment development with which the treatment development initiative hopes to work.

The second paradigm for cognition and schizophrenia studies described by Dr. Fenton was developed by Dr. Patricia Goldman-Rakic through a working memory test of oculomotor-delayed responses in animals. Monkeys are trained to keep the representation of the location of a stimulus in mind and to respond appropriately after delays of varying lengths of time. Through this model, Dr. Goldman-Rakic identified the particular neurons in the prefrontal cortex whose activities seem to be correlated with the ability to retain the memory of the location of the stimulus. Then, using small electrodes and pipettes to examine the effect of different drugs, she found that the level of dopaminergic (D-1) input into this prefrontal cortex circuit greatly affected the efficiency and extent of the animal's working memory. When there is deficient D-1 input, these prefrontal cortical cells cannot function, and the animals cannot perform the delayed-response task. However, because D-1 agonists can cause a great deal of nausea, investigators are searching for a D-1 agonist that can work preferentially in these brain cells, as well as other ways to influence mnemonic activity further down the signaling pathway.

Dr. Fenton observed that treatment development is currently hampered by the absence of adequately reliable and valid measurement tools to assess cognition as a clinical treatment target. To address this gap, the Request for Proposals (RFP) for cognition in schizophrenia was issued, having three major objectives: (1) to catalyze regulatory acceptance of cognition in schizophrenia as a valid target for drug registration; (2) to promote the development of novel compounds to enhance cognition in schizophrenia; and (3) to help focus the economic research power of the pharmaceutical industry on important, but neglected, clinical targets for treatment. These objectives will be met in several ways. NIMH, with academic collaborators at UCLA (which received the contract awarded for this work), will convene a series of six conferences to gain a broad consensus across industry and academia on how to measure cognition as a dependent variable in clinical trials, what kind of clinical trials are appropriate for testing new agents, and which neuropharmacologic models are most promising for discovering potential new targets and ligands. Dr. Fenton reported that he has been negotiating with the FDA about meeting with its Psychopharmacology Advisory Committee to agree on the contract's endpoints and methodologies. To facilitate better collaboration between NIMH and the pharmaceutical industry, the UCLA contractor also will conduct interviews with 50 to 100 large and small drug-production and biotech companies to evaluate the potential for academic investigators to access compound libraries and to work through some of the intellectual property issues. One of the contract deliverables will be a database of potential lead compounds for treating cognitive deficits in schizophrenia. If one of these compounds has a potential human application, the contractors also will conduct a translational proof-of-concept trial.

To conclude his presentation, Dr. Fenton briefly described the newly released RFA pertaining to measuring depression as a dependent variable in clinical trials. This has been another problematic area, he said, because current measures for evaluating depression as a dependant variable in treatment trials are 40 years old and have demonstrated only a 50 percent placebo response rate—showing that neither an agent known to be effective nor its comparison product is superior to placebo. These measures do not appear to be sensitive to new medications and new mechanisms.

In July 2002, NIMH convened more than 110 experts on depression in five workgroups to define the core features of depression and examine the extent to which current measures do or do not capture them (e.g., sleep increase or decrease, weight gain or loss, cognitive impairment, guilt, hopelessness, suicidality, anhedonia, and appetite increase or decrease). Following that meeting, the newly issued RFA on depression assessment called for the creation of five multidisciplinary work teams to focus on different aspects of depression assessment and recommend new or refined evaluation batteries that are more suitable for clinical trials with a variety of participants and therapies for depressive syndromes.

Discussion

Dr. Nemeroff asked whether NIMH might consider convening a 2- or 3-day meeting to review the validity of animal models for psychiatric disorders, because there have been many advances in understanding potential influences on the development of various psychological problems since the last such meeting (e.g., the relationship of early life trauma to mood and anxiety disorders). A new meeting could bring together experts in primate and non-primate models,

models of schizophrenia and anxiety disorders, and preclinical and clinical models, including provocation tests and naturalistic paradigms. Publication of proceedings from such a meeting would benefit the field and help direct intramural and extramural programs at NIMH. When Dr. Fenton agreed that input from Council members and others with in-depth knowledge of particular aspects of this complicated endeavor was always welcome, Dr. Nemeroff offered his continued support and participation.

Dr. Gunnar commented that the treatment development initiative seemed very positive, particularly in the rationale for moving beyond the DSM classification system to understanding the neuroscience underlying the observed symptoms. However, the RFP seems to focus on understanding cognition as a symptom within a syndrome, and the RFA seems to focus on improving the assessment of depression. Perhaps this reflects the difficulty of moving away from syndrome labels to understanding symptoms. Dr. Fenton replied that the solicitations reflect how the FDA looks at these issues. A major question about the cognitive deficit in schizophrenia is whether aspects of it are unique to that disorder or whether some aspects cut across other psychiatric disorders with a cognitive component. One goal of the workshops to be convened under the UCLA contract is to examine this question. If the cognitive deficit turns out to be general to several disorders, the model—in terms of interacting with the FDA—will be similar to one it recently approved for indicators of agitation that appear in numerous disorders. Essentially, a generic indication follows one regulatory path through the FDA, while a disease-specific indication follows another.

Dr. Nestler opined that NIMH could have a major impact in this area. For example, he knows of several pharmaceutical companies that have identified molecules with potential utility for treating the cognitive deficits in schizophrenia but that have not yet applied this knowledge in clinical trials. Moreover, the FDA regulations further complicate decisions about whether to move forward with such trials. With respect to the specificity of cognitive deficits, it is not yet clear whether the cognitive abnormalities in schizophrenia involve unique features compared to cognitive deficits seen in other neurological disorders or whether treatments that are targeted to cognitive deficits in schizophrenia also will improve cognitive deficits seen in other mental illnesses. This issue cannot be resolved until effective molecules are identified for testing in clinical populations.

Dr. Tsuang agreed that dissecting the sub-syndromes of severe mental disorders is an important first step. For example, in treating individuals with schizophrenia, while improving cognition is important, flatness of affect, in terms of amygdala function, also needs to be addressed. To date, no drugs adequately improve this flatness of affect, and NIMH can take a leadership position in developing an animal model for this symptom.

STIGMA AND MENTAL ILLNESS: UPDATE FROM A RECENT WORKSHOP

Dr. Ellen Stover, Director, DMDBA, reported on the status of NIMH research initiatives to reduce the stigma associated with mental illness. NIMH, she said, supported very little research on stigma before 1999. In recent years, however, the definition of stigma has been notably modified and refined by several researchers in ways that make the topic more researchable.

Drs. Bruce Link and Josephine Phelan, deconstructing the components of stigma, found the following:

- Societies only regard certain differences among people as relevant and consequential. For example, among medical conditions, schizophrenia and AIDS are more socially relevant than bone fractures, hypertension, or melanoma.
- Stigma entails both labeling and stereotyping. The label links the person to a set of undesirable characteristics that form the stereotype. In the case of mental illness, the label often evokes images of psychosis or violence.
- Stigma involves the separating of *us* from *them*—a distancing of one group from another that involves both psychological and physical aspects. Thus, for example, research has shown that many people report not wanting to live near or work with people with mental illnesses.
- The negative labels often given to stigmatized individuals result in status loss and discrimination.
- People with power can and do stigmatize others. The lack of parity in mental health insurance coverage, for example, could be viewed as a reflection of this exertion of power.

Turning to the Institute's research portfolio, Dr. Stover pointed out the dearth of studies pertaining to mental illness stigma. While 14 stigma-related grants have been awarded in the area of the basic behavioral sciences, very few have been awarded in the areas of clinical interventions and services.

Recent NIMH initiatives to stimulate stigma research and reduce stigma included:

- An international conference on stigma and global health, co-sponsored with the NIH Fogarty International Center (FIC) in September 2001, after basic scientists at NIH realized that stigma was hampering the conduct of clinical trials and efforts to combat disease on a global level. Almost half of the several hundred scientists convened came from developing countries. Schizophrenia and HIV infection were among the stigmatized disorders of major interest at this meeting.
- After this conference, the FIC, with 11 other partners at NIH, HRSA, the Canadian Institute of Health Research (CIHR), and the International Development Research Center, issued a jointly sponsored RFA to support international research collaborations for the study of stigma and global health. The RFA has a November 2002 receipt date for funding in fiscal year 2003 (see http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-03-001.html).
- Under the leadership of Dr. Emeline Otey, DMDBA formed a Stigma Working Group in 1999 that has commissioned three white papers to address media representations of mental illness, measures to assess stigma, and effective stigma-reduction techniques.
- NIMH staff is participating in a curriculum development project for children in grades 6 to 8 that is entitled "Mental Illness and the Brain" and is designed, in part, to aid in destigmatizing mental illness.
- In conjunction with the Annenberg School for Communications at the University of Pennsylvania, Dr. Otey organized a conference held in July 2002 that focused on the important role of the media in conveying information about mental illness and in contributing to stigma. That meeting revealed that people with mental illness are portrayed on television as nearly 10 times more likely to commit violent acts than the general population. Greater

television watching, according to research data, also is linked to greater intolerance toward those with mental illness. However, the Internet, a key source of information for adolescents, may be a potentially productive venue for future stigma-reduction campaigns.

Dr. Stover emphasized that future initiatives to reduce the stigma associated with mental illness should include more participation by consumers and others affected by mental illness to bring to the discussion more of a real-world perspective. An NIMH-supported researcher in this area, Dr. Patrick Corrigan, has been comparing the relative efficacy of change strategies that involve, respectively, education, personal contact, and protest; he has found that protest is not an effective intervention for reducing stigma.

Mr. James McNulty, Council member and current President of the National Alliance for the Mentally Ill (NAMI), followed Dr. Stover's presentation with some further observations about the July 2002 conference on the media and stigma and the experience of stigma on his own life. He said that, although efforts have been made to reduce the stigma associated with mental illness, much remains to be done and that the conference on stigma was very informative, particularly Dr. Corrigan's research-based recommendations for combating stigma.

Recollecting his own experiences many years earlier in trying to get help for his overwhelming depression, Mr. McNulty said his first encounter with the public mental health system was very discouraging. Although he was well educated and had many other social advantages, he was, at that point, financially impoverished. He encountered numerous roadblocks to obtaining care, and at one point he was told to not be too concerned about seeking treatment because he likely would not recover. Mr. McNulty said that he found that message from a public servant devastating. He managed to get past it by banding together with others who also suffered from mental illnesses and who understood the very real and harmful consequences of stigma, which include discrimination, disability, and, too often, death. Persons with mental illnesses, particularly those with schizophrenia, depression, and borderline personality disorder, have high suicide rates, and the morbidity and mortality associated with eating disorders are not fully appreciated. The stigma associated with mental illness continues to prevent many of those needing mental health treatments from receiving them.

Stigma, continued Mr. McNulty, will not vanish by itself. A particularly impressive aspect of the Council, which he urged Dr. Insel to continue fostering, is its guidance in bringing new ideas into focus. NIMH needs to work in tandem with SAMHSA and CMHS to deliver the proven treatments now available. It is unacceptable that 50 million Americans suffer, at some point in their lives, from some form of mental illness and that many of them never receive treatment. There is no easy answer. Although stigma is a very difficult area to study, pursuing research to reduce the stigma associated with mental illness is a critical part of NIMH's function and one for which necessary resources must be marshaled.

To drive home the sting of stigma in the media, Mr. McNulty displayed a headline from *The Trentonian*, a Trenton, New Jersey, newspaper, describing a fire in the Trenton Psychiatric Hospital (the facility where John Nash, the Nobel Prize-winning mathematician, was a patient). The headline read "*Roasted Nuts*!" This was a terrible message, Mr. McNulty said, to send about people who are suffering from an episode of mental illness. However, a number of

advocates protested this insensitivity and succeeded in getting the publisher of *The Trentonian* to print some educational articles about mental illness. Mr. McNulty encouraged Council members, staff at governmental agencies, and others to work with the media in an effort to reduce the stigma associated with mental illness.

Discussion

Dr. Tsuang, agreeing that one of NIMH's missions is to eradicate stigma, recalled that one successful way to counter the impression that individuals with mental illness are violent and dangerous is to interview real patients in classroom situations. This seems to change the opinions of medical students. Stigma, Dr. Tsuang continued, is a bias fostered by the media. In order to eradicate stigma, he said, we must radically change the perception of mental illness.

Paradoxically, Mr. McNulty replied, some attempts to counter stigma have an unintended rebound effect. For example, public relations experts have tended to think that a celebrity is a useful advocate for many different diseases. Actually, many young people take a cynical view of celebrities who make Public Service Announcements—that they are simply working off some community service debt to society for an infraction. While older people tend to regard celebrities as good spokespersons and tend to trust scientists and doctors, younger people are not similarly impressed.

Dr. Nemeroff mentioned a remarkable program being organized by the Annenberg Foundation in which he has been involved. Dr. Dwight Evans, Chair of the Psychiatry Department at the University of Pennsylvania, and Dr. Kathleen Jamison, Dean of the Annenberg School of Journalism, have been awarded a $10 million grant specifically directed at educating the media about the major classes of psychiatric disorders. Mr. McNulty acknowledged that Dr. Jamison was at the NIMH-sponsored conference in July 2002, and recalled that she had discussed how suicide is dangerously romanticized in the movie "The Virgin Suicides" and how little protest there was in response to this film.

PUBLIC COMMENT

The first speaker in the public comment period, Ms. Valerie Porr, President of the National Association for Personality Disorders (NAPD), said she particularly appreciated NIMH's willingness to tackle the issue of stigma, as borderline personality disorder, which her group focuses on primarily, seems to be more stigmatized than any other mental illness. The national help line operated by NAPD receives reports that some therapists refuse to treat individuals with this diagnosis. Borderline personality disorder often is linked with the stigmatizing term "self-mutilation." Ms. Porr added that because borderline personality disorder is designated by the American Psychiatric Association (APA) as Axis II, it is not covered by most insurance policies. NAPD is trying to change both the name and the assigned DSM Axis for this disorder through a national letter-writing campaign. Recently, Ms. Porr reported, she received a letter from the APA saying it would consider these suggestions as it develops the next edition of the DSM. She asked Council and NIMH to work with the relevant organizations to consider how mental illnesses are named and categorized. Labeling, she concluded, impacts every aspect of the mental health and substance abuse communities. To address these issues, the NAPD is

holding a conference in Bethesda on December 2-3, 2002 (see http://www.mental-health-today.com/borderline/conference.htm), when a panel will discuss strategies to decrease the stigma associated with individuals with borderline personality disorder.

Ms. Joan Zlotnik, Executive Director of the Institute for the Advancement of Social Work Research, joined the praise for Drs. Insel and Nakamura, saying she was impressed by the breadth of NIMH's responsibilities. She noted that an NIMH-sponsored June conference on social work research reinforced the observation that most people with mental illnesses do not have their needs met by the mental health system. Conference participants from the justice, social service, and veterans affairs systems agreed that mental disorders are poorly handled by the mental health and other service delivery systems. While it is important that the partnerships with CMHS, SAMHSA, and other systems work to comprehend the biology of mental illness, the partnerships also need to work to improve the intervention and social service systems and to address the stigma associated with mental illness. For example, one of the conference findings was that mothers who are most likely to lose custody of their children also have severe mental illnesses.

Mr. Donald Fowles, representing the Academy for Psychological Clinical Science (APCS), explained that this relatively new organization grew out of a 1994 conference at Indiana University and that its members represent internships and Ph.D. programs for training clinical scientists. APCS was formed to promote outstanding clinical science training. The issues it deals with are student practicum requirements that leave little time for developing needed expertise in basic research disciplines and making a research career as attractive as alternative opportunities. Mr. Fowles thanked Dr. Nakamura for meeting last March to begin discussions with NIMH about how APCS can be more effective in helping develop the next generation of clinical scientists.

Ms. Cynthia Folcarelli, Executive Vice President of the National Mental Health Association (NMHA), thanked Dr. Nakamura not only for his impressive leadership but also for working overtime to outreach to and collaborate with members of organizations such as the NMHA that represent consumers, families, and other stakeholders with an interest in research. She also welcomed Dr. Insel and his commitment to translating research findings into real-world applications so that people get state-of-the-art treatment. Ms. Folcarelli added her praise for NIMH's willingness to tackle the issue of stigma that has a poisoning effect on all aspects of the mental health field, impacting what research gets funded, what services are delivered, and who can access treatment. Stigma is, indeed, a toxic agent that impedes progress in multiple domains. She also applauded NIMH for examining the mental health response to disaster, noting that DHHS is developing a 5-year strategic plan for homeland security that provides much detail on addressing the physical impact of bioterrorism but provides little detail on addressing the psychological impact of all types of terrorism. She encouraged Council members and NIMH to work with the HHS leadership to address this omission.

Dr. Ritchie concurred that a substantial sum of money was being spent on improved defense systems, with little time devoted to addressing the psychological consequences of chemical or biological attacks or other weapons of mass destruction. She said that preparing appropriate disaster plans to deal with those psychological consequences is vitally important. She cited this

past year's anthrax scare, which, while less devastating than many feared, did temporarily shut down the U.S. Capitol building.

Ms. Dixianne Penney, a family member and co-founder of the year-old National Education Alliance for Borderline Personality Disorder, thanked NIMH for its increased research efforts on borderline personality disorder over the past 5 years and for its willingness to reach out to its constituency of consumers, parents, and community organizations. Ms. Penney also agreed that stigma often inhibits people from speaking out about personality disorders. Continuing research, she added, was the only hope for families to ameliorate the pain, suffering, and loss of human potential associated with personality disorders, and she hoped that Dr. Insel would maintain the current level of investigative efforts.

Ms. Leslie Scallet, representing the Suicide Prevention Action Network, said that the Network was looking forward both to NIMH's development of a research agenda on suicide and suicide prevention as called for in the Surgeon General's report on this issue and to working with Dr. Insel.

Dr. Darrel Regier, Director of the Office of Research at the American Psychiatric Association, extended congratulations to Drs. Zerhouni and Insel on their historic appointments. He said that the APA is very pleased with both selections and will continue to advocate for NIH and NIMH funding. In collaboration with other advocacy groups and organizations, the APA is working very hard to support enactment of mental health insurance parity legislation. The Council workgroup reports on this issue provide strong empirical evidence that this is a feasible action. Dr. Regier reported that he, Dr. Steven Mirin, Executive Director of the APA, and Dr. Paul Appelbaum, President of the APA, had met the week before with the *Washington Post* editorial board to discuss the consequences of the paper's previous opposition to parity legislation and were delighted with an editorial this week endorsing the new House bill. Although enactment is not complete until the President signs the bill, impressive progress towards passage has been made.

Another important event reflecting a collaborative effort between the APA and NIMH staff was the August release of a research agenda for DSM-V at the World Congress of Psychiatry in Yokohama, Japan. The Congress also was notable as the first to focus on depression research and the possible development of a different conceptualization of and a different set of diagnostic criteria for depressive disorders. Council member Dr. Ming Tsuang and NIMH staff members Drs. Dennis Charney and Wayne Drevets were distinguished speakers, along with other U.S. and international investigators. Their presentations addressed all aspects of depression—from preclinical animal models to its epidemiology. The Japanese Congress was the first of a series of research conferences that the APA is proposing.

In response to Ms. Porr's concerns about the stigma attached to borderline personality disorder, Dr. Regier said that planning a conference on stigma at the same time that the research agenda on stigma is coming forward seemed fortuitous. The APA is concerned not only about the validity and reliability of diagnostic criteria, but also about stigma that might be associated with the

names of some disorders. The APA is interested in empirical studies showing whether or not changing a name of a disorder, in fact, reduces the stigma associated with that disorder. The APA expects to use data from such studies for the next iteration of the DSM.

A final issue that Dr. Regier wanted to present was that the only official diagnostic code that will accompany implementation of the Health Insurance Portability and Accountability Act (HIPAA) legislation—and impact Medicare and other insurance reimbursements—is the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and its glossary of definitions. The APA has been actively discussing this issue with the HHS Secretary and with the National Committee on Vital and Health Statistics because the decision could affect how mental disorders are defined for all of medicine and how DHHS-sponsored services are delivered. It would appear that the decision would also be of concern to NIMH.

To a question from Dr. Nestler about what the APA is doing to promote a research agenda, especially in residency training programs, Dr. Regier responded that the APA is collaborating with NIMH and the Institute of Medicine. The chairs of the APA's Council on Research and its Committee on Research Training are currently working with a group from the Association of Residency Training Directors to consider substantial changes that would make research a more integral part of residency training programs. This is a collaborative effort involving NIMH, representatives from the Psychiatry Residency Review Committee, the APA, and a number of academic centers.

Ms. Jerilyn Ross, President and CEO of the Anxiety Disorders Association of America, thanked Dr. Nakamura for his commitment as an interim director, welcomed Dr. Insel, and extended her appreciation to the intramural and extramural programs at NIMH for their extensive work over the past decade on anxiety disorders. Great progress has been made in developing good treatments for these disorders. Unfortunately, too few clinicians are trained to provide established therapies, whether medication or cognitive behavioral therapy, or do not adopt best practices. Because many people are not getting the help they need and deserve, improved dissemination of information about good mental health treatment remains a challenge to be met that Ms. Ross said she hopes would be a high priority for NIMH.

Adjournment

Whereupon, the 201st meeting of the NAMHC adjourned at 1:00 p.m. on September 13, 2002.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

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Richard K. Nakamura, Ph.D., Chairperson